UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,694	08/13/2001	Jan C. Simon	24741-1525	1918

26633 7590 06/03/2003

HELLER EHRMAN WHITE & MCAULIFFE LLP
1666 K STREET,NW
SUITE 300
WASHINGTON, DC 20006

EXAMINER	
DAVIS, RUTH A	

ART UNIT	PAPER NUMBER
1651	19

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,694	SIMON ET AL.	
	Examiner	Art Unit	
	Ruth A. Davis	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-54 and 56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-54 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment filed March 5, 2003 has been received and entered into the case. Claims 36 – 54 and 56 are pending and have been considered on the merits. All arguments have been fully considered.

Claim Objections

Claim objections have been withdrawn due to amendment.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 36 – 45 stand rejected under 35 U.S.C. 103(a) as being unpatentable over The Hypericum Homepage in view of The Merck Manual.

Applicant claims a method for treating a condition selected from cancer, inflammatory skin diseases, precancerous conditions, geriatric skin or microbial skin infections comprising topical administration of an effective amount of a composition consisting of (a) pharmaceutically acceptable carrier and (b) an active agent consisting of (i) hyperforin or (ii) hyperforin and hypericin, to a subject in need thereof. Specifically, the condition is eczema, or is selected from exsiccation eczemas, hyperkeratotic hand/foot eczemas, contact eczemas, atopic dermatitis, neurodermatitis, lichen simplex, prurigo simplex, lymphoma, leukemia, melanoma, epithelial precancerous conditions, tumor metastases or epithelial tumors. The subject is a mammal and the composition is a topical ointment with an effective amount of at least 15 micrograms hyperforin per ml, 0.02 – 20 mg/ml, 1 – 20 mg/ml or 10 mg/ml; or 15 micrograms/ml or 20 – 150 micrograms/ml hypericin.

The Hypericum Home Page (HHP) teaches extracts of Hypericum perforatum (St. John's Wort) include hypericin and hyperforin wherein the extracts exhibit anti-inflammatory and antibacterial effects when externally, or topically, applied (p.3). HHP specifically teaches that hyperforin is attributed with anti-inflammatory and antibacterial effects (p.3).

HHP does not teach a method for treating an inflammatory condition with the claimed effective amounts or the claimed specified conditions. However at the time of the claimed invention, it would have been obvious to one of ordinary skill in the art to use hyperforin and/or hyperforin and hypericin in a method for treating inflammatory conditions because of the

disclosed anti-inflammatory effect. Further, at the time of the claimed invention, it would have been obvious to one of ordinary skill in the art to optimize effective volumes and concentrations as a matter of routine experimentation. Still further, it would have been obvious to one of ordinary skill in the art to include a pharmaceutical carrier because it was routine practice in the art at the time the claimed invention was made. Moreover, at the time of the invention, one of ordinary skill in the art would have been motivated to use hyperforin in a method for treating anti-inflammatory conditions with a reasonable expectation of success because of its known benefit as disclosed by HHP.

HHP does not specifically teach the extracts are effective against eczema, or the other conditions as claimed. However, at the time of the claimed invention, it was well known in the art that eczemas are characterized by inflammation (See "The Merck Manual", cited on PTO-892). Specifically, eczema, contact eczema, atopic eczema, hand and foot eczemas, and lichen simplex are each characterized as superficial inflammations of the skin of varying degrees. In further support, Shroot et al. teaches inflammatory diseases include dermatitis and eczema (col.1 line 12-15) and Lacefield teaches inflammatory conditions include atopic dermatitis, contact dermatitis, eczema, lichen simplex and chronic dermatoses. At the time of the invention, it would have been obvious to one of ordinary skill in the art to treat any of the aforementioned eczemas with hyperforin because of the anti-inflammatory effect as disclosed by HHP. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by HHP and Merck to utilize hyperforin in a method for treating inflammation and eczemas with a reasonable expectation for success.

4. Claims 36, 38 – 43, 36 – 49 and 56 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Valavichyus.

Applicant claims a method for treating a condition selected from cancer, inflammatory skin diseases, precancerous conditions, geriatric skin or microbial skin infections comprising topical administration of an effective amount of a composition consisting of (a) pharmaceutically acceptable carrier and (b) an active agent consisting of (i) hyperforin or (ii) hyperforin and hypericin, to a subject in need thereof. The condition is selected from exsiccation eczema, hyperkeratotic hand and foot eczema, contact eczema, atopic dermatitis, neurodermatitis, lichen simplex, prurigo simplex, lymphoma, leukemia, melanoma, epithelial precancerous conditions, tumor metastases or epithelial tumor. The subject is a mammal. Applicant additionally claims a method of treating cancer comprising administering to a subject in need thereof an effective amount of a composition comprising hyperforin and a pharmaceutically acceptable carrier. The effective amount comprises at least 50 micrograms hyperforin/ml in an injectable form, 100 micrograms/microliter suitable for epicutaneous application, 50 micrograms/ml for systemic administration. The hyperforin is at least 90% pure.

Valavichyus teaches extracts of St. John's Wort, specifically oil extracts, inhibits growth of sarcoma (cancer) cells (abstract). Valavichyus also teaches that administration of the extracts inhibited growth of tumors in animals (or subjects in need thereof). At the time the claimed invention was made, it was known in the art that oil preparations of St. John's Wort are hypericin free and contain high concentrations of hyperforin (See Chavez, p.1622). It was also known in the art that plant oils were used as pharmaceutical carriers.

Valavichyus does not teach the method wherein the claimed volumes and concentrations were used, modes of administration, or wherein the hyperforin is at least 90% pure. However, at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to optimize effective volumes, modes of administration and purity of effective agents as a matter of routine experimentation. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by routine practice to optimize the effective amounts of Valavichyus with a reasonable expectation for successfully treating cancer.

5. Claims 36, 38 – 54 and 56 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Valavichyus in view of HHP and/or DeCosterd.

Applicant claims a method for treating a condition selected from cancer, inflammatory skin diseases, precancerous conditions, geriatric skin or microbial skin infections comprising topical administration of an effective amount of a composition consisting of (a) pharmaceutically acceptable carrier and (b) an active agent consisting of (i) hyperforin or (ii) hyperforin and hypericin, to a subject in need thereof. Specifically, the condition is selected from exsiccation eczema, hyperkeratotic hand and foot eczema, contact eczema, atopic dermatitis, neurodermatitis, lichen simplex, prurigo simplex, lymphoma, leukemia, melanoma, epithelial precancerous conditions, tumor metastases or epithelial tumor. The subject is a mammal, and the composition is a topical ointment and the effective amount is at least 15 micrograms hyperforin per ml, 0.02 – 20 mg/ml, 1 – 20 mg/ml, 10 mg/ml, at least 15 micrograms hypericin/ml or 20 – 150 micrograms hypericin/ml. Applicant additionally claims a method of treating cancer comprising administering to a subject in need thereof an effective amount of a composition

comprising hyperforin and a pharmaceutically acceptable carrier. The effective amount comprises at least 50 micrograms hyperforin/ml in an injectable form, 100 micrograms/microliter suitable for epicutaneous application, 50 micrograms/ml for systemic administration. The cancer is melanoma, lymphoma, skin cancer, mammary carcinoma or leukemia carcinoma and the hyperforin is at least 90% pure.

Valavichyus teaches extracts of St. John's Wort, specifically oil extracts, inhibits growth of sarcoma (cancer) cells (abstract). Valavichyus also teaches that administration of the extracts inhibited growth of tumors in animals (or subjects in need thereof). At the time the claimed invention was made, it was known in the art that oil preparations of St. John's Wort are hypericin free and contain high concentrations of hyperforin (See Chavez, p.1622). It was also known in the art that plant oils were used as pharmaceutical carriers.

The Valavichyus does not teach the method with the claimed volumes/concentrations, modes of administration, or wherein the hyperforin is at least 90% pure. However, at the time of the claimed invention, it would have been well within the purview of one of ordinary skill in the art to optimize effective volumes, modes of administration and purity of effective agents as a matter of routine experimentation. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by Valavichyus and routine practice to optimize the effective amounts of hyperforin with a reasonable expectation for successfully treating cancer.

Valavichyus does not teach the method wherein the cancer is melanoma, lymphoma, skin cancer, mammary carcinoma and leukemia carcinoma. However, HHP teaches extracts of Hypericum perforatum (St. John's Wort) include hypericin and hyperforin wherein the extracts

demonstrate anticancer properties and have been proven to inhibit tumor cells of the brain, lung and skin (p.4). In addition, DeCosterd teaches extracts of Hypericum inhibit growth of colon carcinomas (abstract). Specifically, DeCosterd teaches derivatives of hyperforin exhibit the growth-inhibiting activity (abstract). As evidenced by the cited references, at the time of the invention, hyperforin, derivatives thereof and extracts of Hypericum were well known as effective agents against cancers of various kinds. Although the supporting references do not specifically teach the agents in methods for treating a subject in need thereof, they do suggest that such activity would be expected. Therefore, one of ordinary skill in the art would have been motivated to use the extracts in treating cancers (i.e. lymphoma, mammary and leukemia carcinomas) because of the demonstrated effectiveness in a variety of cancers as disclosed by the references above. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by Valavichyus, HHP and DeCosterd to use compositions comprising hyperforin or hyperforin and hypericin in the methods for treating various cancers with a reasonable expectation of success.

Applicant argues that the HHP does not have publication a date prior to 1998 and that the reference is not from 1996. Applicant additionally argues that there is no motivation to combine the references since there is no recitation of a carrier, and that the carrier provides an unexpected result to the composition.

However, these arguments fail to persuade because HHP clearly has a copyright of 1996. As the reference states, it is an edited version of the publicly available ESCOP (European

Scientific Corporation of Phototherapy), copyright 1996. As such the reference was known or used by others in this country, described in a printed publication, more than one year prior to the date of application. The knowledge was accessible to the public and no attempt was made to keep the information secret.

The Merck Manual is relied upon to demonstrate the state of the art in that the claimed conditions are, by definition, inflammatory conditions. Since such characteristics are intrinsic properties of the claimed conditions, one of ordinary skill in the art would have been motivated by HHP to treat any of the named inflammatory disorders with a reasonable expectation of successfully treating the inflammatory disorders.

Although the references do not teach the claimed amounts or conditions, it would have been well within the purview of one of ordinary skill in the art to determine effective amounts as well as the variety of inflammatory conditions for which known the anti-inflammatory agent hyperforin is effective, as a matter of routine experimentation. Therefore, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by HHP to treat inflammatory skin conditions with hyperforin and/or hyperforin and hypericin with a reasonable expectation of success.

Regarding the absence of a carrier, at the time of the claimed invention, carriers were routinely included in pharmaceutical compositions. At the time of the claimed invention, one of ordinary skill in the art would certainly have been motivated to include a carrier in a pharmaceutical composition as a matter of routine practice.

Regarding applicant's suggestion of unexpected results, the argument fails to persuade because there is no specifically named "unexpected result", and applicant has not provided

supporting evidence thereof. It is further noted that applicant has attributed this unnamed unexpected result to the carrier. This argument is not commensurate in scope with the claims, as there is not a specified carrier or amount thereof, particularly regarding a specific combination that would provide the unnamed "unexpected result".

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruth A. Davis whose telephone number is 703-308-6310. The examiner can normally be reached on M-H (7:00-4:30); altn. F (7:00-3:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 703-308-0196. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ruth A. Davis; rad
May 29, 2003

LEON B. LANKFORD, JR.
PRIMARY EXAMINER